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Docket No 99D-2729

FAX TRANSMISSION COVER SHEET

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These are the comments regarding the f2 statistic

Thank you

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COMMENTS REGARDING DOCKET NO. 97D-2729

Draft Guidance for Industry on BA and BE studies for Orally Administered Drug Products ñ General Considerations; Availability

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The purpose of this document is to provide comments and address concerns about the proposed guidance.

The main concern is the use of the f2 statistic for the comparison of dissolution curves. As demonstrated in Liu, Ma and Chow, (1), this statistic is calculated based on the average of 12 dissolution profiles for each formulation. Thus this statistic is not statistically efficient, e.g. why base the statistic on 12 dissolution curves for each formulation and not 6 pairs since only the means at each sampling point is used and the information regarding between and within data sets is not used. Any inference based on this calculation of f2, then, will not take into account within formulation variability. Ju and Liaw, (2), also point out a disadvantage of the FDA and Chow method: "It is not based on an hypothesis testing procedure, therefore, there is no measurement of the error (Type I or II errors) associated".

The second concern is the subjective selection of the (50,100) acceptance region. Simulation studies, Bartoszynski, Powers and Pultz, (3) indicate the f2 statistic is heavily dependent on intra-assay coefficient of variation. Since the f2 statistic is a function of the numerator of the Rescigno Index, RI, (5), the simulations used these two metrics to compare to the f2. Using 1,000 pairs of profiles from the "same product" with a CV=0.1, f2 and RI agreed, declared different or not different, 979 times out of the 1,000 times, but when CV=0.3 there was only 629 agreement times. In using the interval (50,100) for f2 to declare two products as not different, f2 declared the products different 429 times, i.e. Type I error rate of 0.429, out of 1,000. Therefore, it seems reasonable to expect this acceptance region to be determined either dependent on the actual data collected or for a certain class of drug compounds.

Recent research by Bartoszynski, Powers, Herderick and Pultz, (4) have investigated the use of a non-parametric ranking procedure to compare dissolution curves. This procedure is intuitively appealing because it measures the "distance" between the dissolution curves of the two products, taking into account both the variability of the curves within the curves of the same product and between the two products. There are no underlying assumptions to be satisfied and the only limitation is the two sets of curves must have the same sampling time vector which is really only good experimental design.

Bibliography

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